Drug Class Review
on
Skeletal Muscle Relaxants

Update #2: Preliminary Scan Report #2

March 2008

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #2 Final Report was completed in May 2005 (searches through November 2004). First Preliminary Update Scan Report was completed in February of 2007.

SCOPE AND KEY QUESTIONS:

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different muscle relaxants in reducing symptoms and improving functional outcomes in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of different muscle relaxants in patients with a chronic neurologic condition associated with spasticity, or a chronic or acute musculoskeletal condition with or without muscle spasms?

3. Are there subpopulations of patients for which one muscle relaxant is more effective or associated with fewer adverse effects?

Several aspects of the key questions deserve comment:

Population. The population included in this review is adult or pediatric patients with spasticity or a musculoskeletal condition. We defined spasticity as muscle spasms associated with an upper motor neuron syndrome. Musculoskeletal conditions were defined as peripheral conditions resulting in muscle or soft tissue pain or spasms. We included patients with nocturnal

leg cramps. We excluded obstetric and dialysis patients. We also excluded patients with restless legs syndrome or nocturnal myoclonus.

Drugs. We included the following oral drugs classified as skeletal muscle relaxants: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine. Benzodiazepenes were not considered primary drugs in this report. However, diazepam, clonazepam, and clorazepate were reviewed when they were compared in head-to-head studies with any of the skeletal muscle relaxants listed above. Other medications used for spasticity but considered to be in another drug class, such as gabapentin (a neuroleptic) and clonidine (an antihypertensive), were also only reviewed when they were directly compared to an included skeletal muscle relaxant. Quinine was only included if it was compared to a skeletal muscle relaxant.

The dose of skeletal muscle relaxants used in trials may affect either the efficacy or adverse event profile. One clinical trial[1] of cyclobenzaprine, for example, found equivalent efficacy at 10 and 20 mg tid, but increased adverse events with the higher dose. A study on dantrolene also found a 'ceiling' effect at doses of 200 mg daily, with no increased efficacy but more side effects above that dose.[2] Most trials titrated skeletal muscle relaxants to the maximum tolerated dose or a pre-specified ceiling dose, but there are no standardized methods of titration and determining target doses.

Outcomes. The main efficacy measures were relief of muscle spasms or pain, functional status, quality of life, withdrawal rates, and adverse effects (including sedation, addiction, and abuse). We excluded non-clinical outcomes such as electromyogram measurements or spring tension measurements. There is no single accepted standard on how to measure the included outcomes. Clinical trials of skeletal muscle relaxants have often used different scales to measure important clinical outcomes such as spasticity, pain, or muscle strength.[3] Many trials have used unvalidated or poorly described methods of outcome assessment. Studies that use the same scale often report results differently (for example, mean raw scores after treatment, mean improvement from baseline, or number of patients "improved"). All of these factors make comparisons across trials difficult.

Spasticity is an especially difficult outcome to measure objectively. The most widely used standardized scales to measure spasticity in patients with upper motor neuron syndromes are the Ashworth[4] and modified Ashworth[5] scales. In these scales, the assessor tests the resistance to passive movement around a joint and grades it on a scale of 0 (no increase in tone) to 4 (limb rigid in flexion or extension). The modified Ashworth scale adds a "1+" rating between the 1 and 2 ratings of the Ashworth scale. For both of these scales, the scores are usually added for four lower and four upper limb joints, for a total possible score of 0-32, though scoring methods can vary. Some experts have pointed out that resistance to passive movement may measure tone better than it does spasticity and that the Ashworth scale and other 'objective' measures of spasticity may not correlate well with patient symptoms or functional ability.[6] Other areas of uncertainty regard the significance of the 1+ rating in the modified Ashworth scale and how a non-continuous ordinal variable should be statistically analyzed.[7] An important advantage of the Ashworth scale is that it is a consistent way to measure spasticity or tone across studies, and has been found to have moderate reproducibility. [7] Other measures of spasticity include the pendulum test, muscle spasm counts, and patient assessment of spasticity severity on a variety of numerical (e.g., 1-3, 1-4, 0-4) or categorical (e.g., none, mild, moderate, severe) scales. The best technique may be to perform both objective and subjective assessments of spasticity, but validated subjective assessment techniques of spasticity are lacking.

Muscle strength is usually assessed with the time-honored British Medical Research Council Scale, which is based on the observation of resistance provided by voluntary muscle activity and used in everyday clinical practice.[8] An assessor grades each muscle or muscle group independently on a scale of 0 (no observed muscle activation) to 5 (full strength). This scale was originally devised to test the strength of polio survivors. Data are not available regarding its reliability and validity in assessing spastic and weak patients.

Most studies measure pain using either visual analogue or categorical pain scales. Visual analogue scales (VAS) consist of a line on a piece of paper labeled 0 at one end, indicating no pain, and a maximum number (commonly 100) at the other, indicating excruciating pain. Patients designate their current pain level on the line. An advantage of VAS is that they provide a continuous range of values for relative severity. A disadvantage is that the meaning of a pain score for any individual patient depends on the patient's subjective experience of pain. This poses a challenge in objectively comparing different patients' scores, or even different scores from the same patient. Categorical pain scales, on the other hand, consist of several pain category options from which a patient must choose (e.g., no pain, mild, moderate, or severe). A disadvantage of categorical scales is that patients must choose between categories that may not accurately describe their pain. The best approach may be to utilize both methods.[9] Pain control (improvement in pain) and pain relief (resolution of pain) are also measured using visual analogue and categorical scales.

Studies can evaluate functional status using either disease-specific or non-specific scales. These scales measure how well an individual functions physically, socially, cognitively, and psychologically. Disease-specific scales tend to be more sensitive to changes in status for that particular condition, but non-specific scales allow for some comparisons of functional status between conditions. The most commonly used disease-specific measure of functional and disability status in patients with multiple sclerosis, for example, is the Kurtzke Extended Disability Status Scale (EDSS).[10] The EDSS measures both disability and impairment, combining the results of a neurological examination and functional assessments of eight domains into an overall score of 0-10 (in increments of 0.5). The overall score of the EDSS is heavily weighted toward ambulation and the inter-rater reliability has been found to be moderate. [10] Disease-specific scales are also available for fibromyalgia,[11, 12] low back pain, cerebral palsy, and other musculoskeletal and spastic conditions.

Scales that are not disease-specific include the Medical Outcomes Study Short Form-36 (SF-36), Short Form-12 (SF-12), or another multi-question assessment. Another approach to measuring function is to focus on how well the medication helps resolve problems in daily living that patients with spasticity or musculoskeletal conditions commonly face, such as getting enough sleep or staying focused on the job. Some studies also report effects on mood and the preference for one medication over another.

The following adverse events were specifically reviewed: somnolence or fatigue, dizziness, dry mouth, weakness, abuse, and addiction. We also paid special attention to reports of serious hepatic injury.[13] The subcommittee considered these the most common and potentially troubling adverse events in clinical practice. We recorded rates of these adverse events as well as rates of discontinuation of treatment due to a particular adverse effect. In some studies, only "serious" adverse events or adverse events "thought related to treatment medication" are reported. Many studies do not define these terms. We recorded any information about abuse and addiction, and rates of death and hospitalization when available.

Withdrawal rates. Because of inconsistent reporting of outcomes, withdrawal rates may be a more reliable surrogate measure for either clinical efficacy or adverse events in studies of

skeletal muscle relaxants. High withdrawal rates probably indicate some combination of poor tolerability and ineffectiveness. An important subset is *withdrawal due to any adverse event* (those who discontinue specifically because of adverse effects).

Study types. We included controlled clinical trials to evaluate efficacy. The validity of controlled trials depends on how they are designed. Randomized, properly blinded clinical trials are considered the highest level of evidence for assessing efficacy.[14] Clinical trials that are not randomized or blinded or that have other methodologic flaws are less reliable. These are also discussed in our report with references to specific flaws in study design and data analysis.

Trials comparing one skeletal muscle relaxant to another provided direct evidence of comparative efficacy and adverse event rates. Trials comparing skeletal muscle relaxants to other active medications or placebos provided indirect comparative data.

To evaluate adverse event rates, we included clinical trials and large, high-quality observational cohort studies. Clinical trials are often not designed to assess adverse events, and may select patients at low risk for adverse events (in order to minimize dropout rates) or utilize methodology inadequate for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time, utilize higher quality methodologic techniques for assessing adverse events, or examine larger sample sizes. We did not systematically review case reports and case series in which the proportion of patients suffering an adverse event could not be calculated.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (January 2007 through March 2008) using terms for included drugs and limiting to English-language trials conducted on humans. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 18 potentially relevant citations. Of those, there were no new, potentially relevant studies. In the previous preliminary update scan, four potentially relevant studies were identified (Table 1). Of those, upon second review, Childers 2005, Mathew 2005, and Taricco 2006 were excluded and reasons for exclusion are listed in the table below. This leaves only the Ketenci 2005 trial, an active-controlled trial of tizanidine vs thiocolchicoside, available to be added if this review was selected for a full update. However, the addition of this trial would not be anticipated to significantly impact the previous conclusions as there already exist a number of head-to-head trials including tizanidine in this population.

Table 1. Trials identified in previous preliminary update scan

Author Year	Treatment	Notes
Childers 2005	*Cyclobenzaprine monotherapy vs cyclobenzaprine-plus-ibuprofen*	*Excluded: Focus is on add-on ibuprofen*
Ketenci 2005	Thiocolchicoside vs tizanidine	Low back pain associated with spasm
Mathew 2005	*Diazepam vs placebo*	*Excluded: diazepam only included as a comparator drug*
Taricco 2006	*Multiple SMR's*	*Cochrane review: already included and hasn't been updated since 2000*

New Drugs

Cyclobenzaprine (Amrix) Extended Release Oral Capsule 15mg, 30mg strengths: Approved 2/1/07
Carisoprodol (Soma) Oral Tablet 250mg: Approved 9/13/2007

New Indications

No new indications were identified.

New Safety Alerts

There were a few new FDA safety alerts issued since our last scan related to SMR's and they are listed in the table below:

SMR	Date	Alert type	Focus
Carisoprodol	9/07	Label Change: Warnings, Precautions and Adverse Reactions	Risk of sedative properties, drug dependence, withdrawal and abuse
Tizanidine	4/07	Label Change: Contraindications and warnings	When administered with fluvoxamine or ciprofloxacin (CYP1A2 inhibitors), the serum concentration of tizanidine was significantly increased and potentiated its hypotensive and sedative effects